Biochimica et Biophysica Acta 1853 (2015) 3126–3131

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamcr

Review

Neuronal and metastatic cancer cells: Unlike brothers☆

Paul Heine [a], Allen Ehrlicher [b], Josef Käs [a,*]

[a] Soft Matter Physics Group, Institut für experimentelle Physik I, Leipzig University, Linnestraße 5, D-04103 Leipzig, Germany
[b] Department of Bioengineering, McGill University, Montreal H3A 0C3, Canada

ARTICLE INFO

Article history:
Received 24 March 2015
Received in revised form 10 June 2015
Accepted 12 June 2015
Available online 26 June 2015

Keywords:
Cancer
Invasiveness
Neuronal
Motility
Cytoskeleton
Filopodia

ABSTRACT

During development neuronal cells traverse substantial distances across the developing tissue. In the mature organism, however, they are bound to the confines of the nervous system. Likewise metastatic cancer cells have the potential to establish auxiliary tumor sites in remote tissues or entirely different organs. The epithelial–mesenchymal transition is the transformation of proliferative cancer cells into a highly invasive state, which facilitates the crossing of tissue boundaries and migration across various environments. This review contributes a first look into the parallels and contrasts between physical aspects of neuronal and metastatic cancer cells. This article is part of a Special Issue entitled: Mechanobiology.

1. Introduction

Even though neuronal and cancer cells have quite different purposes in the body, both must traverse substantial distances in the body. It is not wholly identified why neurons can only navigate within the confines of a defined microenvironment, while cancer cells are able to migrate through diverse settings. Recent studies of these cells have revealed some striking similarities in both form and function of these two unique cell types; however the respective roles of these elements have not been thoroughly considered. Here we review these different findings and inspect which aspects are shared between cancer and neuronal cells and how they employ these features for both dissimilar and shared purposes. Specifically, we examine substrate effects particularly in respect to extracellular matrix (ECM) modifications and constrictions, intracellular mechanics, cellular pushing forces, cytoskeletal filaments, and filopodia of neuron and cancer cells, explaining how these unique cell types achieve their specialized purposes, while sharing a variety of features. This will provide a perspective on cellular flexibility in organisms and could unite efforts in two important applied research fields across a variety of disciplines including biology, physics, chemistry and medicine.

Neuronal cells in the developing brain of most organisms do not come into existence pre-wired but are rather laid out in developmental sheets of cells that must be correctly interconnected for proper neuronal function. In this highly intricate process the soma, or cell body, of neurons extends dendrites and axons; these are responsible for conducting electrical impulses and thereby transmit information. During pathfinding in the developing brain they are headed by a motile cytoskeletal structure composed of a dense actin filament network interspersed with microtubule (MT) filaments and a variety of motor proteins. This dynamic neurite tip is called the growth cone and is responsible for seeking out the neuron's synaptic target. Neurites navigate through dense and heterogeneous tissue, which requires a highly specialized motility apparatus [1]. The distinctive combination of long-range navigation through a crowded and diverse environment and their shared developmental aspects are bridging the extremes between metastatic cancer cells and neurons.

When cancer cells spread from their primary tumor to propagate in remote tissue they form metastases, which is the cause of approximately 90% of cancer-related fatalities [2]. For cancer cells to metastasize several physical changes are required. Initially they have to obtain a migratory phenotype and invade adjacent tissues, while chemotaxis leads them to blood vessels. Here they have to penetrate the compact basement membrane ECM by forming protrusive processes with ECM-degrading function and enter the surrounding endothelial cell barrier in order to intravasate into the lymphatic or blood vessels for transport to remote organs or tissues [3].

While cancerous cells can migrate in diverse surroundings, believed to be attributed to their various potential motility modes during the epithelial–mesenchymal transition (EMT), neurites are constricted to the confines of the nervous system.

2. Substrates

Contrary to most other cell types neurons actually prefer to extend on softer over stiffer substrates (Fig. 1, A), but depending on the nervous

☆ This article is part of a Special Issue entitled: Mechanobiology.

* Corresponding author.
E-mail address: jkaes@physik.uni-leipzig.de (J. Käs).

http://dx.doi.org/10.1016/j.bbamcr.2015.06.011
0167-4889/

system type they maneuver through very unlike environments and thereby need to adapt their biomechanics to their surroundings [4].

An example of this can be seen in a study comparing dorsal root ganglion (DRG) cells as a model for the peripheral nervous system (PNS) and hippocampal neurons, which represent neurons of the central nervous system (CNS). It is observed that DRG neurons produce the longest extensions on substrates with a stiffness of ~1000 Pa while higher and lower elasticities reduce outgrowth, whereas hippocampal neurons have a neurite length independent of substrate stiffness. DRGs on soft substrates generate significantly higher forces, while exhibiting greatly reduced retrograde flow rates and stronger cytoskeletal substrate coupling, yet both types of neurons increase their traction forces on stiffer substrates [5].

A similar adaption has also been found in cancer cells, where a variety of cancer cell lines could be categorized as either substrate rigidity-dependent or independent. Substrate stiffness-independent cell lines exhibited no change in growth rate, whereas dependent cell lines displayed increased growth, migration and spreading on stiffer matrices (Fig. 1, B). This stands in stark contrast to other cell types like epithelial, smooth muscle and fibroblasts that are reliant on a narrow range of stiff substrate elasticity for growth. Some of the cell lines that showed a rigidity-dependent growth profile even adapted various hallmarks of the invasive mesenchymal phenotype on stiffer substrates [6].

A possible purpose for this selective behavior is suggested by investigating the originating tissue of these cells, as it has been shown that single cell populations of the MBA-MD231 breast cancer cell line provide characteristic cellular feedback dependent on substrate rigidity. These cancer cells exhibit increased proliferation and invasiveness on substrates with an elasticity and coating comparable to their in vivo metastases sites, an effect known as tissue tropism, suggesting that part of site-specific invasion is determined by local substrate mechanics [7].

Glioblastoma multiforme a highly aggressive cancer of the CNS displays behavior resembling both cancer and neuronal cells depending on ECM rigidity. At low rigidity close to brain tissue (80 Pa) these cells resemble neurons, are largely non-proliferative and display little migration. On stiffer substrates, these cells multiply five-times faster and their migratory speed increases drastically, likely as a result of their transformation from a uniformly rounded morphology with nonfunctional filopodial extensions to a spread and crawling cell [8].

This increased activity on more rigid substrates is also observed in various carcinoma cells: in hepatocellular carcinoma proliferation is increased up to 12-fold on 12 kPa versus 1 kPa matrices, depending on cell type. Treatment with apoptosis-inducing chemotherapeutic drugs showed reduced apoptotic behavior for cells cultured on stiff substrates; however cells cultured on soft matrices had a significantly increased frequency of clone-initiation, a measure of a cell's ability to proliferate indefinitely, pointing to the fact that non-rigid substrates elicit stem cell characteristics in these cells [9].

Increased substrate rigidity can not only stimulate proliferation and chemotherapeutic resistance but also increase cell forces independent of cell spreading, given that the overall net traction forces of both metastatic cells and non-metastatic cells are higher on surfaces having tumor-like stiffness (5 kPa). This could render cell force generation to be a potential candidate as a biomechanical marker for metastatic potential; since metastatic cells exert significantly greater forces than non-metastatic cells, contractile forces can reflect the metastatic phenotype and may function as an in vitro diagnostic [10].

Not all features discussed here might be applicable to cells in 3D in vivo or in vitro environments, since it is plausible that cell form and function might change substantially in this setting.

3. Confinement

Apart from substrate rigidity, other environmental cues transform the motility of neurons and cancer cells. A prominent example of this is the neuron migration along radial glial cells during neurogenesis. This exceptional pathway allows neurons to reach their precise target neuronal layers via enveloping of glial fibers with a leading process, composed of lamellipodia and short filopodia, while the cell assumes a bipolar form and connects the soma to the fiber. This soma-based movement is quite remarkable since neurons in the adult mammalian brain are usually rather stationary, whereas only neurites rearrange themselves [11].

An analogous phenomenon can be observed in certain types of cancer cells whose motility seems to be guided by collagen fibers. Metastatic variations of these cells appear to migrate towards blood vessels and intravasate to eventually form secondary tumors [3]. ECM fiber alignment thus creates motility paths for both neurons and cancerous cells to migrate in a directed way.

In vitro similar tracks for cells can be artificially constructed by creating patterns ranging from 1.5 to 12 μm in grooves, to which various ligand proteins can be applied, which then make up guidance channels. Confining growth cones to these narrow channels of different widths does not alter their movement speed, even though their size adjusts to the channel width. They do however respond to immediate changes in their surroundings, as their extension speed temporarily increased in the nodes between confinement channels. Growth and curiously

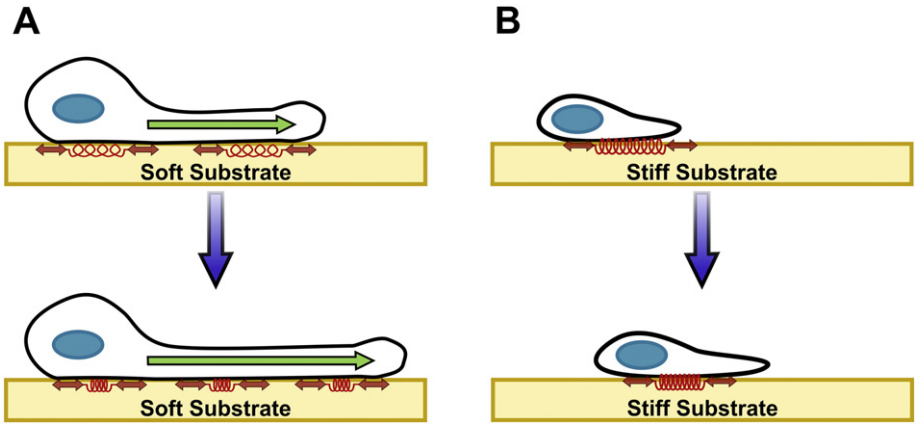

Fig. 1. Diverse motility modes. A) The soft environment on which neurons grow transforms most of the motile forces exerted by the cell into substrate deformation resulting in a fairly static soma. This does not affect growth cone mobility, since it is from this stationary point that stiff microtubules extend into the neurite to provide the pushing forces for translocation. B) On stiff substrates less energy is transferred into substrate deformation, which results in highly motile cancer cells. Not depicted here is the case of cancer cells on soft substrates in which they enter an immobile but highly proliferative state.

pausing phases in outgrowth did not drop, even though they seem redundant in such confinements [12]. In contrast to this both fibroblasts and epithelial cells showed a significantly increased migration velocity along comparable tracks. The transition to a uniaxial phenotype is the most probable cause for this speed increase, as protrusion is no longer hindered by inefficient trailing edge retraction as is the case for well-spread cells [13].

Similar micro-architectures have also been employed to evaluate the motile and invasive response of cancer cells. An assay to evaluate the two possible polarization states permeation (i.e. entering a narrowing channel) and repolarization (i.e. turning around) by analyzing cell migration from large 15 μm into 4 μm channels in various tapering gradients revealed that highly metastatic cells have a more permeative nature than their non-metastatic siblings in steep gradients. There is however also an innate phenotypic heterogeneity of invasiveness in a single cell population, since one cell line displays subpopulations of permeating and repolarizing nature [14].

These highly compressive microenvironments induce a compressive stress within tumor cells and it has been shown that this can facilitate tumor progression. Cells can undergo a phenotype transformation under compression; whereby they actively adapt their morphology to the intracellular stresses generated by cellular distortions as a result of a changing external matrix. This metamorphosis manifests in leader cells that have larger contact areas and more pronounced filopodia, which leads to increased outgrowth and stimulated collective migration [15].

Recognizing that both neurons, depending on their developmental state, and cancer cells can adapt to and exploit environmental rigidity, a connection between these environmental cues and the inner workings of cells has to be established.

4. Pushing forces and intracellular mechanics

Having established that neurons show increased outgrowth on substrates mimicking their softer in vivo environmental stiffness the question arises of whether neurons of the CNS are confined to its boundaries or have the ability to invade the PNS. An investigation of retinal ganglion cells and the growth cones of NG108-15 neuroblastoma cells revealed that their forward pushing forces are not sufficient to penetrate stiffer tissues. AFM measurements also exposed that these neurons are very soft structures with a Young's modulus of ~37 Pa and 80 Pa respectively, which is simply not stiff enough to withstand the involved pressure, as they operate at their structural limit and higher forces could tear them apart. Since brain capillary endothelial cells are a magnitude stiffer than neurons, endothelial cells pose a physical obstacle. Conversely the white and gray matter of the brain have similar elasticities to neurons, provide a much more compliant and thus permeable substrate for neurons [16,17].

The cell motility reaction to these environmental mechanics is revealed in the force–velocity relation, which describes how the cell velocity changes in response to a physical force restraining the cell in the following phases: initially the velocity decreases upon first surface contact with the resisting force; as this force is increased, the velocity continues to decrease exponentially until the stall force is reached, at which point cell movement stops. To understand this force–velocity relationship the underlying dynamics of the actin cytoskeleton have to be considered: first even small forces are sufficient to drastically slow down actin-polymerization driven lamellipodium motion, while actomyosin driven contraction in the back still moves the cell forward. In consequence filaments in-between these regions bend and shorten, which cascades into a stronger conveyed forces towards the back exemplified through increased retrograde actin flow which compensates for polymerization in this halted state. In consequence this lamellipodial stiffness adaption via filament length tuning assures that external forces can be attuned for in the course of navigation, since the adjustment rate is set by the filament cross-linking rate which is comparable to the cell speed [18].

This dynamic remodeling of the actin cytoskeleton is also a prerequisite for metastasis, where an all-encompassing modification of cellular function is necessary to adapt its states of migration, invasion, in/extravasation at defined points in carcinogenesis. During relatively unobstructed migration a dense network of shorter actin filaments branched in 70° is far more dynamic to deal with obstacles as filaments can bend away and still polymerize rather than being stopped head-on as would be the case for perpendicularly-oriented filaments like those found in filopodia. Filopodia however become instrumental when penetrating the environment such as discovering optimal adhesion targets when navigating through a dense 3D cell layer. In these environments filopodia and, their ECM degrading siblings, invadopodia become virtually indistinguishable and a combination of sensory action to identify optimal pathfinding and consequent ECM degradation through protease delivery in their tips can ensure successful tissue invasion [19].

In fact this adaptiveness of the actin filaments making up the lamellipodium accounts for a wide variety of motion seen throughout most eukaryotic cells. These lamellipodial dynamics differ strongly in different cell types ranging from strong stochastic fluctuations at the lamellipodial edge between protrusion and retraction phases in growth cones, reduced fluctuations in wound healing fibroblasts, and almost no fluctuations in highly motile fish keratocytes. In order to achieve this incredible range of motile states in different cells the lamellipodium needs to stochastically switch between an engaged and disengaged filament polymerization, as well as change the rate of polymerization and retrograde flow. The large amount of fluctuations in neuronal growth cones allows for superior probing of its environment and the detection of miniscule amounts of guidance cues, by quickly transforming its cytoskeleton to correct for guidance errors [20].

Following nerve injury growth cones soften and increase in area accompanied by a reduction in actin content and increase in tubulin, ultimately resulting in increased regenerative outgrowth rates [21]. Highly metastatic cancer cells also harbor a less dense cytoskeleton and have a softer microenvironment compared to less invasive or benign cells. An evaluation of intracellular particle transport exposed increased particle motion powered by active processes as well as increased particle fluctuations [22]. Novel measurements of aggregate forces in the cytoplasm of benign and malignant breast cancer cells via force-spectrum-microscopy indicate that malignant cells not only have a ~30% smaller cytoplasmic stiffness, but also exhibit three times higher intracellular forces. This increased cytoplasmic activity, actuated through molecular motor activity, corresponds well to the observation of increased proliferation and higher traction forces in malignant cells [23]. These properties render metastatic cells highly dynamic, a cytoskeletal prerequisite for the invasive tasks required during tissue invasion, in carrying out massive morphological changes.

Generally cancer tissue is much stiffer than benign tissue; however, individual cancerous cells are much softer. Likewise magnetic tweezer measurements showed that more invasive cancer cells are up to ten-times more compliant than their non-invasive equivalents. Cancer cells of a given tumor population also possess different rigidities possibly suggesting a diverse array of roles in tumor progression. Furthermore application of pharmacological substances to increase/decrease cell stiffness also leads to less/more invasive potential [24,25].

Immense cellular changes also occur during the EMT where epithelial tumor cells de-differentiate, undergo vast morphological changes, and take on a motile and invasive phenotype. This transformation is complemented by improved resistance to many forms of cell death and aging, rendering it indispensable for the initiation of new tumors [26].

5. Microtubules

All of these morphological transformations and reactions are powered by the cell cytoskeleton, where research has for many years

focused on actin filaments as a main contributor to motility; however, MTs are also crucial for proper cell function. In *Drosophila* neurons MTs have been shown to be absolutely critical for the initial outgrowth of developing neurites. Neurite elongation has been assumed to be powered by a combination of pushing through MT polymerization and pulling by actin-related mechanism; though, initial extension is solely driven by MT sliding through kinesin-1 molecular motors [27].

Another essential MT-associated motor protein is dynein, which has recently been shown to bulk push the MT cytoskeleton forward during axonal elongation and its disruption leads to a substantial increase in neuronal tension and induces retraction [28]. One conceivable way the motor protein might achieve this is through the capture and subsequent pushing of MTs at the cell-cortex. The directional sliding of MTs is possible due to a very high turnover of dynein-complex associations which enjoy a very high probability of interacting with short MTs [29]. Super-resolution imaging revealed that forward translocation of the MT network by cortical actin association is vastly dependent on calcium activity, which seems to be a vital contribution to the process of nucleokinesis that makes up soma-based neuron migration [30].

However precisely this close cytoskeletal association between actin and MTs can also result in growth cones coming to a resting state or even retracting. When folding filopodia in the periphery confine the MT extension machinery and confine their expansion in the growth cone, neurite advancement goes into an intermediate-term mode of growth regulation [31]. In this process and during general phases of growth cone motility MTs are bent significantly and an analysis of deformation and buckling behavior has disclosed that the stored bending energy contributes significantly to the total protrusion force. Local variations of stored bending energy and deviations in MT orientation and consequent interference with retrograde flow also appear to directly influence navigational growth cone extension (Fig. 2, A) [32].

In cancer cells MTs are a compelling target for chemotherapy since they are imperative to the process of mitosis and cell division and a variety of drugs have been used to target their dynamics. The rapid course of mitosis requires highly dynamic MTs during all stages of its cycle and research has shown that even low concentrations of antimitotic drugs can suppress these dynamics without altering overall MT mass or even target the vascular blood supply of tumors [33].

In invasive cancer cells the formation of ventral membrane protrusions such as invadopodia has been implicated in cell invasion. An investigation on the invasiveness of breast cancer cells in 3D Matrigels revealed the emergence of short protrusions, reminiscent of invadopodia, and long protrusions which seem to originate from their smaller siblings. Tubulin monomers were only found in longer protrusions and treatment with a MT-stabilizing agent suppressed their formation and also decreased cell invasiveness all the while leaving invadopodia intact [34].

This suggests that MTs might play a crucial role in later phases of invasion, while invadopodia are vital early on. A recent innovative study employed low doses of a MT-stabilizing agent, usually used in cancer treatment, to reduce scarring after spinal cord injury in rodents. The drug activated MT polymerization in the tip of the neurite and simultaneously reduced scar formation by inhibiting meningeal fibroblast motility. The combination of these effects reinitiated neuronal polarization and axon extension through the now less inhibitory glial scar tissue resulting in a functional treatment of the injured CNS [35].

6. Intermediate filaments

The role of actin and MT filaments in migration through dense tissue is relatively well understood, while the contribution of various intermediate filaments remains to be identified. Intermediate filaments might not contribute directly to cellular locomotion; however, recent advances revealed that they serve auxiliary functions in invasion during EMT of cancer cells. Members of the keratin and vimentin family and specifically their co-expression have been implicated in stimulation of invasive and metastatic capacity in melanoma and breast cancer [36,37]. Specially-engineered keratin-free murine keratinocytes astonishingly show roughly 60% higher deformability and are far more invasive than wild-type keratinocytes. These results are particularly fascinating when taking into account that during the EMT keratins are down-regulated, while vimentin is up-regulated and cancer cells adopt an invasive migratory behavior [38]. While the systemic keratin/vimentin switch is necessary for metastatic behavior in cancer cells, neuron-specific intermediate filaments could similarly be a secondary factor for proper function. In neurons intermediate filaments are the most abundant cytoskeletal element in the form of neurofilaments, which far exceed the number of MTs. These filaments fill a pivotal role in expanding the width of mature axons and increasing neurite conduction velocity [39–41].

7. Filopodia

In tumor metastasis one cellular structure consistently gains more infamy within the scientific community, invadopodia. This unpleasant cousin of the filopodia is also a fingerlike membrane protrusion that is formed on the ventral surface of cancer cells. One of its functions is to focus matrix metalloproteinases which are used to break down the basement membrane, which forms the barrier between epithelial and stromal compartments. Overpowering this boundary is crucial in the establishment of metastases of remote organs: after invadopodia form they intrude into the basement membrane, extend and mature, and eventually guide the cell into the subsequent compartment (Fig. 2, B). The development of these structures is a three-step process that initially

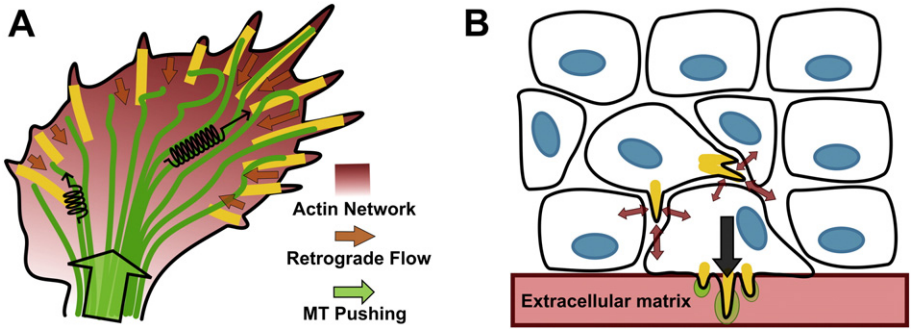

Fig. 2. Different uses for filopodia (indicated in yellow). A) In this illustration of a neuronal growth cone filopodial density is increased on the right and comparatively more MTs are aligned with filopodia or bend by the retrograde flow. When polymerizing MTs reach the edge they contribute directly to extension. When they oppose the retrograde flow and get deformed they store bending energy, as denoted by the large spring, and drive actin polymerization leading to edge extension. On the left side fewer filopodia provide structural guidance to MTs and they do not reach as far into the periphery, leading to less deformation and consequently less stored energy. The combination of these effects leads to a net advancement on the right side of the growth cone. B) In cancer cells filopodium-like protrusions serve not only as wedge-like force mediators to squeeze through their microenvironment, but also as focal points for matrix metalloproteinases secretion (indicated through green ellipses) which break down the basement membrane to facilitate intravasation.

is solely relying on the actin cytoskeleton and filopodium/lamellipodium-associated proteins, while later outgrowth is reliant on filopodial actin and once matured MTs and vimentin are required to augment extension [42]. Alternative proteolytic arrangements are formed in the situation of 3D tissue invasion. Pseudopods are located anterior to the leading edge, while small actin-rich protrusions develop transiently on the lateral cell body. This zone partition indicates an archetype of proteolytic-based cell migration in which adhesion and traction to the ECM is established by the cell front, while the neighboring zones of proteolytic structures degrade the ECM [43].

After induction of the EMT in human carcinoma cell lines their cell motility as well as adhesion to 2D substrates was increased, while in 3D cultures their growth rate was diminished. They did however develop invasive protrusions that were mostly supported by MTs, similar to those found in stable EMT cells, which were not blocked by matrix metalloproteinases inhibitors [44]. The secretion of these matrix degrading enzymes allows invadopodia to spatially expedite the rearranging of ECM fibrils, which makes room for motility tracks that promote 3D cell migration. When this ability is blocked invadopodia become functionally similar to filopodia and cells are forced to wedge themselves through the fibrils similar to amoeboid motion, thereby encountering intense deformations on their cytoskeleton and nucleus (Fig. 2, B) [45].

In fact an increased amount of filopodial extensions is a characteristic of invasive carcinoma cells, which can also be enhanced by upregulation of the filopodial actin bundling protein Fascin. Increased expression of Fascin correlates with higher invasivity and consequently higher occurrences of metastases and poor prognosis for patients. Upregulating Fascin presence also increases motility in both regular and cancer cells through its actin bundling abilities which generates filopodia and long-spiky actin protrusions (invadopodia) [46]. Other filopodium-inducing proteins like Formins, WAVE proteins, the ENA/VASP protein family and the Arp2/3-complex are expressed in a variety of cancer cells and have also been implicated in cancer progression and invasion into 3D environments through their synergistic effects in filopodia formation [47].

Characteristic filopodial features such as length and density also seem to be affected by substrate rigidity in cancer cells. When cultured on softer environments they retract at a slower rate and thereby form more and longer filopodia, this seems to be regulated by myosin II contractile activity which intensifies with increasing substrate stiffness. The adaption of more pronounced filopodia in softer surroundings allows cancer cells to more thoroughly probe for environmental cues in migration, while cells in harder regimes can conserve this energy for alternative tumor-related tasks such as division and malignant transformation [48].

Astonishingly neurons were recently also found to form actin-based protrusions that were structurally and functionally similar to invadopodia. Their structures extended radially alongside microtubules within the central growth cone domain. In in vitro motoneuron axons they employ a variety of matrix metalloproteinases in their tips for local matrix degradation to exit the spinal cord and grow out into the periphery [49].

Naturally neurons employ filopodia as a pathfinding feature for their ability to sense guidance molecules through inherent receptors, this then triggers attractive/repulsive responses through cytoskeletal reorganization. In mice lacking focal adhesion kinase, which mediates N-WASP as an actin nucleation-promoting factor, filopodial motility is disturbed which impairs their outgrowth, morphology, neuronal connectivity and function [50]. However while navigation is slowed in growth cones lacking filopodia it is not completely abolished, which is also the case for some other cell types that naturally employ filopodia [51]. Retarded neurite outgrowth also occurs naturally when RGCs undergo a developmental switch in growth cone dynamics after birth. An increased filopodial adhesion and decreased lamellar protrusion area severely limits their growth rate through the introduction of inactive states when pausing or retracting [52].

Just how important filopodia are for guided neurite extension is illustrated in our measurements of their distribution and density in turning events of NG108-15 neurites, where more than twice the number of filopodia extended on the turning side of the growth cone. This effect is likely mediated by the mechanical interactions of MTs and filopodia in the periphery (Fig. 2, A). When the filopodial density is in the concentrated regime (for rigid-rods) on the extending side of the growth cone spontaneous alignment occurs due to volume exclusion effects, because filopodia have roughly the same bending rigidity as MTs and can be assumed as rigid-rods.

8. Concluding remarks

This review provides a first look into the similarities and differences between physical aspects of neuronal and cancerous cell lines. Due to the complexity and range of involved systems this is not a comprehensive comparison, but is intended to begin a discussion on the valuable lessons that might be learned from comparing these unique cell types in the course of their development.

Conflict of interest

The authors declare no conflict of interest

References

[1] K. Franze, P.A. Janmey, J. Guck, Mechanics in neuronal development and repair, Annu. Rev. Biomed. Eng. 15 (1) (2013) 227–251.
[2] D. Spano, C. Heck, P. De Antonellis, G. Christofori, M. Zollo, Molecular networks that regulate cancer metastasis, Semin. Cancer Biol. 22 (3) (Jun. 2012) 234–249.
[3] W. Wang, J.B. Wyckoff, V.C. Frohlich, Y. Oleynikov, S. Hüttelmaier, J. Zavadil, L. Cermak, E.P. Bottinger, R.H. Singer, J.G. White, J.E. Segall, J.S. Condeelis, Single cell behavior in metastatic primary mammary tumors correlated with gene expression patterns revealed by molecular profiling, Cancer Res. 62 (21) (Nov. 2002) 6278–6288.
[4] L.A. Flanagan, Y.-E. Ju, B. Marg, M. Osterfield, P.A. Janmey, Neurite branching on deformable substrates, Neuroreport 13 (18) (Dec. 2002) 2411–2415.
[5] D. Koch, W.J. Rosoff, J. Jiang, H.M. Geller, J.S. Urbach, Strength in the periphery: growth cone biomechanics and substrate rigidity response in peripheral and central nervous system neurons, Biophys. J. 102 (3) (Feb. 2012) 452–460.
[6] R.W. Tilghman, C.R. Cowan, J.D. Mih, Y. Koryakina, D. Gioeli, J.K. Slack-Davis, B.R. Blackman, D.J. Tschumperlin, J.T. Parsons, Matrix rigidity regulates cancer cell growth and cellular phenotype, PLoS ONE 5 (9) (Sep. 2010) e12905.
[7] A. Kostic, C.D. Lynch, M.P. Sheetz, Differential matrix rigidity response in breast cancer cell lines correlates with the tissue tropism, PLoS ONE 4 (7) (Jul. 2009) e6361.
[8] T.A. Ulrich, E.M. de J. Pardo, S. Kumar, The mechanical rigidity of the extracellular matrix regulates the structure, motility, and proliferation of glioma cells, Cancer Res. 69 (10) (May 2009) 4167–4174.
[9] J. Schrader, T.T. Gordon-Walker, R.L. Aucott, M. van Deemter, A. Quaas, S. Walsh, D. Benten, S.J. Forbes, R.G. Wells, J.P. Iredale, Matrix stiffness modulates proliferation, chemotherapeutic response, and dormancy in hepatocellular carcinoma cells, Hepatology 53 (4) (Apr. 2011) 1192–1205.
[10] C.M. Kraning-Rush, J.P. Califano, C.A. Reinhart-King, Cellular traction stresses increase with increasing metastatic potential, PLoS ONE 7 (2) (Feb. 2012) e32572.
[11] U.E. Gasser, M.E. Hatten, Central nervous system neurons migrate on astroglial fibers from heterotypic brain regions in vitro, Proc. Natl. Acad. Sci. U. S. A. 87 (12) (Jun. 1990) 4543–4547.
[12] M.S. Smirnov, K.A. Cabral, H.M. Geller, J.S. Urbach, The effects of confinement on neuronal growth cone morphology and velocity, Biomaterials 35 (25) (Aug. 2014) 6750–6757.
[13] A.D. Doyle, F.W. Wang, K. Matsumoto, K.M. Yamada, One-dimensional topography underlies three-dimensional fibrillar cell migration, J. Cell Biol. 184 (4) (Feb. 2009) 481–490.
[14] M. Mak, C.A. Reinhart-King, D. Erickson, Microfabricated physical spatial gradients for investigating cell migration and invasion dynamics, PLoS ONE 6 (6) (Jun. 2011) e20825.
[15] J.M. Tse, G. Cheng, J.A. Tyrrell, S.A. Wilcox-Adelman, Y. Boucher, R.K. Jain, L.L. Munn, Mechanical compression drives cancer cells toward invasive phenotype, Proc. Natl. Acad. Sci. 109 (3) (Jan. 2012) 911–916.
[16] T. Betz, D. Koch, Y.-B. Lu, K. Franze, J.A. Käs, Growth cones as soft and weak force generators, Proc. Natl. Acad. Sci. 108 (33) (Aug. 2011) 13420–13425.
[17] T. Fuhs, L. Reuter, I. Vonderhaid, T. Claudepierre, J.A. Käs, Inherently slow and weak forward forces of neuronal growth cones measured by a drift-stabilized atomic force microscope, Cytoskeleton (Hoboken, N.J.) 70 (1) (Jan. 2013) 44–53.
[18] J. Zimmermann, C. Brunner, M. Enculescu, M. Goegler, A. Ehrlicher, J. Käs, M. Falcke, Actin filament elasticity and retrograde flow shape the force–velocity relation of motile cells, Biophys. J. 102 (2) (Jan. 2012) 287–295.

[19] D. Vignjevic, G. Montagnac, Reorganisation of the dendritic actin network during cancer cell migration and invasion, Semin. Cancer Biol. 18 (1) (Feb. 2008) 12–22.
[20] M. Knorr, D. Koch, T. Fuhs, U. Behn, J.A. Käs, Stochastic actin dynamics in lamellipodia reveal parameter space for cell type classification, Soft Matter 7 (2011) 3192–3203.
[21] M. Martin, O. Benzina, V. Szabo, A.-G. Végh, O. Lucas, T. Cloitre, F. Scamps, C. Gergely, Morphology and nanomechanics of sensory neurons growth cones following peripheral nerve injury, PLoS ONE 8 (2) (Feb. 2013) e56286.
[22] N. Gal, D. Weihs, Intracellular mechanics and activity of breast cancer cells correlate with metastatic potential, Cell Biochem. Biophys. 63 (3) (Jul. 2012) 199–209.
[23] M. Guo, A.J. Ehrlicher, M.H. Jensen, M. Renz, J.R. Moore, R.D. Goldman, J. Lippincott-Schwartz, F.C. Mackintosh, D.A. Weitz, Probing the stochastic, motor-driven properties of the cytoplasm using force spectrum microscopy, Cell 158 (4) (Aug. 2014) 822–832.
[24] A. Fritsch, M. Höckel, T. Kiessling, K.D. Nnetu, F. Wetzel, M. Zink, J.A. Käs, Are biomechanical changes necessary for tumour progression? Nat. Phys. 6 (10) (Oct. 2010) 730–732.
[25] V. Swaminathan, K. Mythreye, E.T. O'Brien, A. Berchuck, G.C. Blobe, R. Superfine, Mechanical stiffness grades metastatic potential in patient tumor cells and in cancer cell lines, Cancer Res. 71 (15) (Aug. 2011) 5075–5080.
[26] N. Tiwari, A. Gheldof, M. Tatari, G. Christofori, EMT as the ultimate survival mechanism of cancer cells, Semin. Cancer Biol. 22 (3) (Jun. 2012) 194–207.
[27] W. Lu, P. Fox, M. Lakonishok, M.W. Davidson, V.I. Gelfand, Initial neurite outgrowth in *Drosophila* neurons is driven by kinesin-powered microtubule sliding, Curr. Biol. 23 (11) (Jun. 2013) 1018–1023.
[28] D.H. Roossien, P. Lamoureux, K.E. Miller, Cytoplasmic dynein pushes the cytoskeletal meshwork forward during axonal elongation, J. Cell Sci. (Jun. 2014) jcs.152611.
[29] T. Mazel, A. Biesemann, M. Krejczy, J. Nowald, O. Müller, L. Dehmelt, Direct observation of microtubule pushing by cortical dynein in living cells, Mol. Biol. Cell 25 (1) (Jan. 2014) 95–106.
[30] B.I. Hutchins, S. Wray, Capture of microtubule plus-ends at the actin cortex promotes axophilic neuronal migration by enhancing microtubule tension in the leading process, Front. Cell. Neurosci. 8 (2014) 400.
[31] P. Rauch, P. Heine, B. Goettgens, J.A. Käs, Different modes of growth cone collapse in NG 108-15 cells, Eur. Biophys. J. 42 (8) (Aug. 2013) 591–605.
[32] P. Rauch, P. Heine, B. Goettgens, J.A. Käs, Forces from the rear: deformed microtubules in neuronal growth cones influence retrograde flow and advancement, New J. Phys. 15 (1) (Jan. 2013) 015007.
[33] M.A. Jordan, L. Wilson, Microtubules as a target for anticancer drugs, Nat. Rev. Cancer 4 (4) (Apr. 2004) 253–265.
[34] K. Kikuchi, K. Takahashi, WAVE2- and microtubule-dependent formation of long protrusions and invasion of cancer cells cultured on three-dimensional extracellular matrices, Cancer Sci. 99 (11) (Nov. 2008) 2252–2259.
[35] J. Ruschel, F. Hellal, K.C. Flynn, S. Dupraz, D.A. Elliott, A. Tedeschi, M. Bates, C. Sliwinski, G. Brook, K. Dobrint, M. Peitz, O. Brüstle, M.D. Norenberg, A. Blesch, N. Weidner, M.B. Bunge, J.L. Bixby, F. Bradke, Systemic administration of epothilone B promotes axon regeneration after spinal cord injury, Science (Mar. 2015) aaa2958.
[36] M.J.C. Hendrix, E.A. Seftor, Y.-W. Chu, K.T. Trevor, R.E.B. Seftor, Role of intermediate filaments in migration, invasion and metastasis, Cancer Metastasis Rev. 15 (4) (Dec. 1996) 507–525.
[37] M.J. Hendrix, E.A. Seftor, R.E. Seftor, K.T. Trevor, Experimental co-expression of vimentin and keratin intermediate filaments in human breast cancer cells results in phenotypic interconversion and increased invasive behavior, Am. J. Pathol. 150 (2) (Feb. 1997) 483–495.
[38] K. Seltmann, A.W. Fritsch, J.A. Käs, T.M. Magin, Keratins significantly contribute to cell stiffness and impact invasive behavior, Proc. Natl. Acad. Sci. 110 (46) (Nov. 2013) 18507–18512.
[39] S.R. Gill, P.C. Wong, M.J. Monteiro, D.W. Cleveland, Assembly properties of dominant and recessive mutations in the small mouse neurofilament (NF-L) subunit, J. Cell Biol. 111 (5 Pt 1) (Nov. 1990) 2005–2019.
[40] J.P. Julien, Neurofilament functions in health and disease, Curr. Opin. Neurobiol. 9 (5) (Oct. 1999) 554–560.
[41] P.C. Monsma, Y. Li, J.D. Fenn, P. Jung, A. Brown, Local regulation of neurofilament transport by myelinating cells, J. Neurosci. 34 (8) (Feb. 2014) 2979–2988.
[42] M. Schoumacher, R.D. Goldman, D. Louvard, D.M. Vignjevic, Actin, microtubules, and vimentin intermediate filaments cooperate for elongation of invadopodia, J. Cell Biol. 189 (3) (May 2010) 541–556.
[43] K. Wolf, P. Friedl, Mapping proteolytic cancer cell–extracellular matrix interfaces, Clin. Exp. Metastasis 26 (4) (2009) 289–298.
[44] J. Oyanagi, T. Ogawa, H. Sato, S. Higashi, K. Miyazaki, Epithelial–mesenchymal transition stimulates human cancer cells to extend microtubule-based invasive protrusions and suppresses cell growth in collagen gel, PLoS ONE 7 (12) (Dec. 2012) e53209.
[45] S. Kumar, V.M. Weaver, Mechanics, malignancy, and metastasis: the force journey of a tumor cell, Cancer Metastasis Rev. 28 (1–2) (Jun. 2009) 113–127.
[46] L.M. Machesky, A. Li, Fascin: invasive filopodia promoting metastasis, Commun. Integr. Biol. 3 (3) (May 2010) 263–270.
[47] A. Arjonen, R. Kaukonen, J. Ivaska, Filopodia and adhesion in cancer cell motility, Cell Adhes. Migr. 5 (5) (2011) 421–430.
[48] Y.-R. Liou, W. Torng, Y.-C. Kao, K.-B. Sung, C.-H. Lee, P.-L. Kuo, Substrate stiffness regulates filopodial activities in lung cancer cells, PLoS ONE 9 (2) (Feb. 2014) e89767.
[49] M. Santiago-Medina, K.A. Gregus, R.H. Nichol, S.M. O'Toole, T.M. Gomez, Regulation of ECM degradation and axon guidance by growth cone invadosomes, Dev. Camb. Engl. 142 (3) (Feb. 2015) 486–496.
[50] M.R. Chacón, A.I. Navarro, G. Cuesto, I. del Pino, R. Scott, M. Morales, B. Rico, Focal adhesion kinase regulates actin nucleation and neuronal filopodia formation during axonal growth, Development 139 (17) (Sep. 2012) 3200–3210.
[51] A. Wacker, H. Gerhardt, L.-K. Phng, Tissue guidance without filopodia, Commun. Integr. Biol. 7 (2014) e28820.
[52] M.B. Steketee, C. Oboudiyat, R. Daneman, E. Trakhtenberg, P. Lamoureux, J.E. Weinstein, S. Heidemann, B.A. Barres, J.L. Goldberg, Regulation of intrinsic axon growth ability at retinal ganglion cell growth cones, Invest. Ophthalmol. Vis. Sci. 55 (7) (Jul. 2014) 4369–4377.